TOPICAL PREPARATIONS CONTAINING CYCLOSPORIN

TECHNICAL FIELD

The present invention relates to topical preparations containing cyclosporin as a major active component. The topical preparations containing cyclosporin include topical preparations in the form of an emulsion or a non-emulsion.

The term "cyclosporin"referred to in this application is intended to mean a single substance or a mixture of a group of cyclosporin antibiotics which are described in detail in Japanese Patent Laid-open Publication (kokai) No. 2-17,127.

BACKGROUND ART

Cyclosporin is known as an immune inhibitor and it has extensively been employed in the field of the transplant of organs including the kidney. Recently, cyclosporin becomes apparent as being effective to various diseases that are caused mainly from autoimmune reaction, in addition to the efficacy for the transplant of the organs. A number of literature has already been published which reports the efficacy of cyclosporin forarthritis. Autoimmune diseases to which cyclosporin has been applied or proposed to be applied may include, for example, autoimmune blood diseases, chronic bronchial asthma, systemic erythematosus, polymyositis, systemic scleroderma, Wegner syndrome, myasthenia gravis, psoriasis vulgaris, autoimmune intestinal diseases (idiopathic ulcerative colitis, Crohn disease), sarcoidosis, multiple sclerosis, juvenile diabetes mellitus, uveitis, psoriatic rheumatoid, glomerulonephritis, and the like.

As described hereinabove, cyclosporin contributes largely to the inhibition of rejection at the time of transplanting organs and autoimmune therapy; however, it is also known that it may often cause severely adverse affect upon the kidney when administered orally over a long period of time so that this toxicity to the kidney has been the cause of suppressing cyclosporin from being extensively employed. It can be noted that there are many cases where morbid states are caused to occur at the skin, eye or joint to which topical preparations can be applied. In the case of diseases that can be administered with topical preparations, it is advantageous to avoid systemic administration that might cause disturbances to occur in the kidney. If the focus of a disease is restricted to a layer of the dermis, topical administration through the epidermis is more advantageous than other ways of administration because it can save the amount of a medicine to be administered and further the efficacy of the medicine can be enhanced in association with a local rise in the concentration of the medicine, while systemic side effects can be reduced. The way of administration in the form of topical preparations can be said to be one of the most effective drug delivery systems (DDS) for cyclosporin.

On the other hand, it is extremely difficult to formulate cyclosporin into topical preparations so as to maintain its highly therapeutical effect, unlike watersoluble or low-molecular weight, pharmaceutically effective substances. One of the reasons for this difficulty is because the cyclosporin is a large cyclopolypeptide having a molecular weight of larger than 1,200 so that it suffers from the difficulty in allowing cyclosporin to infuse or penetrate through the horny skin layer into the focal site present in the dermis layer. Another reason for the difficulty is because the cyclosporin is insoluble in water and there is the restriction upon the kind of organic solvents in which the cyclosporin

can be dissolved. As such specific organic solvents, a lower alkanol such as ethanol or isopropanol may be generally employed. However, such a lower alkanol is too highly irritative to the skin when it is employed for topical preparations in a relatively high concentration, so that safe topical preparations cannot be provided. On the other hand, when the lower alcohol is employed in a relatively low concentration for topical preparations, the ability of the cyclosporin to be dispersed uniformly in the topical preparations may be impaired, thereby providing no topical preparations with a highly therapeutical effect.

Reports on clinical research of cyclosporin ointments have been published to the effect that a 10% cyclosporin formulation may be pharmaceutically effective or ineffective, so that its pharmaceutical effects may or may not be reproduced. Some reports describe specific compositions of cyclosporin formulations yet no clear pharmaceutical effects therefor are described.

For example, Japanese Patent Laid-open Publication No. 2-17,127 discloses compositions which contain, as essential components, cyclosporin and a mono- or polyunsaturated fatty acid or an unsaturated alcohol, each having from 12 to 24 carbon atoms. The mono- and polyunsaturated fatty acids may include, for example, vaccenic acid, linoleic acid, linolenic acid, elaidic acid, erucic acid, and the like. The unsaturated alcohol may include, for example, vaccenyl alcohol, linoleyl alcohol, linolenyl alcohol, elaidyl alcohol, erucyl alcohol, and the like. Further, it describes the compositions are effective to various skin diseases; however, that publication does not specify its pharmaceutical effects and refers merely to the ability of the cyclosporin to infuse or penetrate through the skin and to the concentration of the cyclosporin. The publication is thoroughly silent about the extent, for example, to which the cyclosporin is effective against psoriatic diseases.

Several cases of skin diseases are reported; many of the literature states that cyclosporin is effective against the skin diseases.

For example, atopic dermatitis is reported in Acta. Derm. Venerol.: Suppl. 144, 136–138 (1989) where an alcoholic oily gel of containing cyclosporin at the rate of 10% by weight is effective against atopic dermatitis. Further, Arch. Derm.: 125, p. 570 (1989) reports that an alcoholic oily gel of a 10% (by weight) cyclosporin is effective.

There are reports of contact-type dermatitis, for example, in Arch. Dermato-1: 125, 568 (1989) which reports to the effect that cyclosporin is employed for a human DNCB test with no effect. Further, Contact Dermatitis: 19, 129–132 (1988) makes a review on three formulations: a 10% cyclosporin formulation in Labrafil (polyoxyl-5-oleate, olive oil and ethanol), a 5% cyclosporin formulation in castor oil, and a 5% cyclosporin formulation in castor oil containing 20% propylene glycol; however, it states the results of this review are not so satisfactory that a more effective solvent is required. In addition, Contact Dermatitis, 20, 155–156 states that none of three formulations, or 0.1%, 1% and 10% cyclosporin formulations, are effective at all against contact dermatitis.

Pharmaceutical effect of cyclosporin upon psoriasis is described, for example, in Clin. Res., 34, 1007A (1986), in which it is described that topical administration of cyclosporin is not effective for the therapy to psoriasis, although neither the concentration of cyclosporin nor the composition thereof are specified. It is also described in Lancet, 1, 806 (1987) that a 2% by weight cyclosporin (on ointment base) is as effective upon psoriasis as placebo.